Attorney Docket No. 1017751-000031

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP APPEAL BRIEF - PATENTS**
Guy Couaraze et al.	Group Art Unit: 1616
Application No.: 10/031,949	Examiner: Andriae M Holt
Filed: May 1, 2002	Appeal No.: _____
For: LOW-DOSE TABLETS AND PREPARATION PROCESS	

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is from the decision of the Primary Examiner dated December 7, 2009 finally rejecting claims 3-6 and 8-18, which are reproduced as the Claims Appendix of this brief.

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The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

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I. Real Party in Interest

The present application is assigned to Ethypharm. Ethypharm is the real party in interest, and is the assignee of Application No. 10/031,949.

II. Related Appeals and Interferences

The Appellant legal representative, or assignee, does not know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 3-6 and 8-18 are pending, and stand rejected, and are the subject of this appeal. Claims 1, 2, and 7 are cancelled.

IV. Status of Amendments

All amendments have been entered. There are no outstanding or newly offered after-final amendments.

V. Summary of Claimed Subject Matter

Independent claim 11 is directed to a tableting premix (p. 14, l. 5-10) for the preparation of a tablet (p. 10, l. 22-30), said premix consisting essentially of: (a) between 99 and 100% by weight of neutral microgranules coated with an active

principle mixture (p. 14, l. 5-10), wherein said active principle mixture consists essentially of an active principle and an optional binder (p. 19, l. 5-10), and said neutral microgranules consist essentially of 62.5% to 91.5% sucrose and the remainder starch (p. 7, l. 18-22), and (b) between 0 and 1% by weight of a lubricant (p. 12, l. 33-36), and wherein the premix is directly compressible (p. 14, l. 5-10).

Independent claim 17 is directed to a tablet consisting essentially of: neutral microgranules coated with an active principle mixture, and an excipient (p. 10, l. 22-30; p. 11, l. 9-14; p. 12, l. 28-31), wherein: a) the neutral microgranules consist essentially of 62.5% to 91.5% sucrose with the remainder starch, are spherical of uniform diameter between 100 and 2000 µm (p. 7, l. 18-34; p. 12, l. 15-17), and are directly compressible (p. 7, lines 18-34; p. 14, l. 5-10); b) the coating of active principle mixture consists essentially of an active principle and an optional binder (p. 19, l. 5-10) such that the active principle is less than 40 mg/g of the tablet (p. 13, l. 13-19); and c) the excipient is a compression excipient at less than 1% by weight of the tablet (p. 12, l. 28-31).

Independent claim 18 is directed to a tablet consisting essentially of: neutral microgranules coated with an active principle mixture, an excipient (p. 10, l. 22-30; p. 11, l. 9-14; p. 12, l. 28-31), and a film coating over the tablet (p. 13, l. 35-38), wherein: a) the neutral microgranules consist essentially of 62.5% to 91.5% sucrose with the remainder starch, are spherical of uniform diameter between 100 and 2000 µm (p. 7, l. 18-34; p. 12, l. 15-17), and are directly compressible (p. 7, lines 18-34; p. 14, l. 5-10); b) the coating of active principle mixture consists essentially of an active principle and an optional binder (p. 19, l. 5-10) such that the active principle is less than 40 mg/g of the tablet (p. 13, l. 13-19); c) the excipient is a compression excipient at less than 1% by weight of the tablet (p. 12, l. 28-31); and d) the film

coating on the tablet restricts exposure of the active principle to light, moisture, or oxygen; or modifies release of the active principle; or modifies the color or appearance of the tablet; or any combination thereof (p. 13, l. 35-38; p. 14, l. 1-3).

VI. Grounds of Rejection to be Reviewed on Appeal

Claims 11-12 stand rejected as anticipated under § 102(b) in view of Bhutani (US Pat 4684516)

Claims 11-12 stand rejected as anticipated under § 102(b) in view of Harrison. (US Pat 4806361)

Claims 3-6 and 8-18 stand rejected under § 103(a) as unpatentable over Frost (WO 88/02629) and Makino (US Pat 4983399).

Applicants traverse each of the foregoing rejections; and appeal and seek review and reversal of all outstanding rejections.

VII. Argument

The subject matter of the instant invention is a low dose pharmaceutical formulation that is directly compressible into a stable, durable tablet while eliminating compression diluents, excipients, disintegrants, and protective coatings.

The formulation is a collection of: neutral microgranules, an active principle mixture coating on the microgranules, and an optional lubricant at low concentration (≤1%). The formulation surprisingly eliminates the need for an additional compressible diluent (Spec., p. 10, lines 22-30), or other protective or enteric coatings or layers of dispersant on the active principle-coated particles (e.g., Spec., p 10, lines 4-20) . The ultimate dosage form, i.e., tablet, may, however, be coated

with a film. *See, e.g.,* Specification, p. 13, l. 35, and claim 18. The instant claims expressly exclude such added diluents, adjuvants, layers, or coatings as a component of the particles themselves.

More specifically, the claimed formulations include only: neutral microgranules, an active principle mixture of only the active principle and an optional binder; and 0-1% lubricant. The specification explains that one objective is the development of a tablet comprising a low dose of active principle on microgranules, and wherein the microgranules themselves are the compressible diluent thereby eliminating the need for any additional coating agents to modify release of active agent or mask its taste. Specification, p. 10, lines 22-30. The claimed invention is significant as much for what the formulation excludes as for what it includes. This is a principal distinction over the cited references, and particularly Bhutani and Harrison.

Bhutani

Bhutani describes pharmaceutical formulations that are fundamentally different than the claimed invention. Bhutani describes high dose formulations of neutral microgranules coated with active principle, but which are configured to include added layers of retardants and/or disintegrants. Bhutani's inclusion of such added layers produces different particles, and thus different formulations, and as such Bhutani does not teach or suggest the low dose, directly compressible formulations of the instant claims.

Bhutani describes a controlled release pharmaceutical formulation wherein an active ingredient is coated on non-pareil beads, or onto drug crystals or granules (col 4, lines 11 to 13); and wherein the resulting pellets are then coated with varying

amounts of a retarding material, and are then still further coated with several layers of disintegrating agent or agents (col 4, lines 20 to 24).

Bhutani talks of controlled release coatings that permit single, individual dosage forms that include high - rather than low - dosages. Col. 5, lines 3-4; *see also* col. 5, lines 10-20 (stating that lower volume of disintegrant permits greater volume of medicament). The result being that "two or three normal doses of a drug in the form of coated pellets may be incorporated into one tablet which may be taken only once every eight to twelve hours." Col. 3, lines 58-61.

Bhutani distinguishes his invention over prior art medicaments by highlighting the fact that the art fails to describe a "uniform coating of a retarding material on a medicament-containing particle overlaid with a uniform coating of disintegrant material and then compressed into a dense tablet that breaks up quickly in the body." (col. 3, lines 44-48); *see also* col. 5, lines 4-10 ("As distinguished from the prior art tablets in which the disintegrant is mixed with the medicament-containing beads, the present invention is more efficient in that it allows smaller amounts of disintegrant to be used by providing a thin, uniform coating of the disintegrant on the medicament-containing bead."). Bhutani thus emphasizes the importance of those added layers on the individual particles that retard dissolution or otherwise control the manner or location in the body in which the active agent is released. There is no corresponding element in the subject matter of the instant claims. Indeed, the instant claims expressly exclude such elements. Thus, Bhutani does not teach each and every element of the claimed invention, and in fact teaches away from it.

Bhutani describes the importance of the coating on the individual particles in emphasizing that an important advantage of his formulations is that "the compressed tablet can be bisected on upper, or lower, or both sides of the tablets which make it

easier to administer one-half tablet or one-half dose, something which is impossible when coated pellets are dispensed in gelatin capsules. Col. 4, lines 1-6. Thus, Bhutani expressly teaches that the particles themselves must be coated so that when the tablet is bisected, the retardant effect is maintained. This is to be distinguished from the instant claim 18, wherein the film coating is on the tablet, per se, not the individual particles. As such, the critical coatings of the Bhutani reference are expressly excluded by the instant claims, and Bhutani does not teach the claimed invention.

Further, Bhutani speaks of the advantages of the reduced volume of disintegrant in the described formulations. Col. 5, lines 10-20. Even though the volume is reduced, one skilled in the art reading Bhutani would clearly understand that Bhutani is teaching that the disintegrant is an essential component, otherwise why would Bhutani strive to reduce its volume rather than simply eliminate it. According to Bhutani, the use of such a disintegrant is critical. Such a disintegrant, however, is excluded by the express language of the instant claims. Thus, Bhutani fails to teach the claimed invention, but instead teaches away from it.

The formulations of Bhutani further include substantial quantities of various other agents, excipients and adjuvants, even before they are coated with the final "retarding" layer or layers and/or disintegrants. These are added to the tablets both contemporaneously with the active principle mixture, and as a series of separate and discrete coatings over the active principle mixture. The examples recite addition of a "coating powder" that includes both an active principle and, e.g., 5% talcum powder (Examples 1, 3-5, 7, 9-11), or 5% povidone (Examples 2, 6, 8). Once that coating powder containing the active principle and talcum powder or povidone is applied, and dried, two "final coatings" are added, i.e., talcum powder (Examples 1-11).

Those excipients are excluded by the instant claims ("the excipient is a compression excipient at less than 1% by weight of the tablet." Claim 17; *see also* claim 18 and claim 11 [0-1% compression excipient]).

The materiality of the foregoing distinctions is evident from the instant specification. Applicants explained that references such as Bhutani were distinguishable over the claimed invention in that such prior art formulations describe modified release formulations wherein the active principle-coated microgranules require further polymer coatings to control the release of the active principle. Specification, p. 10, lines 5-11. Applicants explained that such added layers fundamentally alter the characteristics of the formulations and confer entirely different compressibility and tableting behavior. Specification, p. 10, lines 13-16. For that reason, Applicants explained, the teachings of those references were inapplicable to formulations such as those claimed here. Specificaton, p. 10, lines 16-20. From its earliest stages, the instant application expressly distinguished those more complicated formulations, and the claims have consistently excluded such behavior-modifying components.

The instant claims expressly require that 99-100% of the formulation is neutral microgranules coated with active principle (and optional binder), and wherein any remainder (≤1%) is lubricant. Thus, the claimed tablets and/or tableting premix expressly exclude the added components required by Bhutani, and the claimed invention is novel over Bhutani.

Harrison

Applicants likewise traverse the rejection of claims 11-12 as anticipated by Harrison. As above, Harrison describes a formulation wherein beads of an inert

particulate core are coated with an active agent, which is then further coated with a complex combination of polymers. Harrison, Col. 3, lines 48-68 ("This invention provides a sustained-release unit dosage form of a medicament ... for oral administration comprising beads composed of an inert particulate core having adhered thereto a coating comprising said medicament, wherein each bead of said medicament-coated inert particulate core is surrounded by a sustaining coating comprising at least three admixed polymers..." emphasis added); *see also* col. 5, lines 12 to 14; and col. 6, lines 21-47.

Each of Harrison's active agent-coated beads is further coated with a "sustaining coating" comprising at least three polymers. The thee polymers must be carefully selected to be soluble at various and distinct pH ranges. Col. 3, lines 48-68; *see also* col. 5, lines 15-53. Harrison teaches that the selection and proportionate composition of those polymers in creating the coating is important in achieving the uniform release of the medicament (e.g., col. 4, lines 53-56); and that the rate of release of the medicament can be still further modified by adjustment of the thickness of the sustaining coating and the ratios of the three polymers (col. 5, lines 54-59). Thus, Harrison teaches that those polymers are essential components of the Harrison formulation.

As argued above with respect to Bhutani, the presently claimed formulation expressly excludes, and thus does not accommodate, the sustaining coatings and the various polymers required by the teachings of the Harrison reference. Harrison does not teach how to make formulations that exclude those elements, much less formulations that can be directly compressed into stable, durable tablets. Thus, Harrison fails to provide a teaching of formulations having the elements of the instant claims, and so Harrison fails to anticipate the subject matter of claims 11-12.

Non-obviousness

Frost & Makino

The rejection asserts that claims 3-6 and 8-17 would have been obvious to one of ordinary skill in the art in view of Frost over Makino. Applicants traverse the rejection, and request reversal. Frost and Makino fail to teach or suggest the claimed invention, whether taken alone or together. Further, they are both directed to fundamentally distinct objectives, neither of which is applicable here.

Here again it is worthwhile to revisit the subject matter of the instant claims. The claims recite specific formulations for low dose, directly compressible tablets. They are as significant for what they exclude as for what they include. As shown above, the instant specification makes it clear that the prior art formulations are complicated by the presence of other excipients and adjuvants. Thus, for example, claim 17 distinguishes over the prior as being limited to a tablet consisting essentially of: neutral microgranules coated with an active principle mixture, and less than 1% excipient; and claim 18 as directed to a similar tablet, but wherein a film coating is applied over the tablet - as opposed to the individual beads.

Frost is directed to a dosage form for the administration of 2', 3'-didesoxyadenosine (DDA) for the treatment of AIDS. The formulation includes DDA protected by one or more pharmaceutically inert layers, at least the outer one of which is stable in acidic pH and which dissolves in basic pH. This prevents the DDA from being exposed to gastrointestinal fluids until reaching the small intestine (p. 2, lines 1-8).

There are various embodiments. In one, there is a plurality of dosage subunits having three components: the active agent, DDA; pharmaceutically inert-

acid resistant layers; and an inert layer, e.g., nonpareil seeds. Those subunits are described as suitable for inclusion in a capsule; or in a matrix for formation into a compressed tablet (p. 2, lines 9-15). The matrix disintegrates in the GI tract to release the plurality of dosage subunits.

Frost describes tablets that include a matrix of a polymer such as hydroxypropylmethylcellulose. The hydroxypropylmethyl-cellulose constitutes from about 5 to about 40% of the formulation (p.3, line 23-p. 4, line 12). Frost teaches that such a polymer is included as an "outer pharmaceutically inert component stable in acidic pH which dissolves in basic pH" to control exposure and release of the active agent. *See, e.g.,* p. 1, lines 15-24; p. 2, lines 16-27; p. 2, line 28-p. 3, line 7; and p. 3, lines 15-22, and lines 27-34.

Frost does not teach a tablet consisting essentially of neutral microgranules coated with only an active principle mixture, and only 1% or less of a compression excipient. On the contrary, Frost teaches that very substantial quantities of a "sustained release matrix", e.g., hydroxypropylmethylcellulose (p. 1, lines 10-13), is essential in the formulations described therein. Thus, although Frost teaches that the formulations can be compounded into tablets, just as with Bhutani and Harrison, those formulations require substantial additional ingredients that deviate substantively from the express language of the instant claims. Because the instant claims expressly exclude such sustained release agents as are required by Frost, the reference fails to teach or suggest the claimed invention, and instead actually teaches away.

Nor can it be argued that the hydroxypropylmethylcellulose of Frost can be equated with the optional binder of the instant claims. In the instant claims, the optional binder must be included in the active agent premix (claim 11) or active

principle mixture (claims 17 & 18). In contrast, Frost consistently and repeatedly characterizes the hydroxypropylmethylcellulose as a separate "outer pharmaceutically inert component." *See, e.g.,* p. 1, lines 15-24; p. 2, line 28-p. 3, line 7; and p. 3, lines 15-22, and lines 27-34. In one of Frost's alternative embodiments, the active principle is "sandwiched between pharmaceutically inert layers, at least the outer of which is stable in acidic pH and which dissolves in a basic pH." p. 1, line 33 - p. 2, line 4. In other embodiment, Frost describes it as a separate "barrier component to shield the 2', 3'-didesoxyadenosine from the gastrointestinal fluids." p. 2, lines 16-27. Thus, Frost expressly teaches that such a component is a component separate and distinct from the active agent layer, and one that overlies and protects the active agent mixture. As such, that component cannot be interpreted as the optional binder of the instant claims, and is expressly excluded by the instant claims.

Finally, Applicants take exception to the argument that Frost teaches the use of hydroxypropylmethylcellulose at 1%. In Example VII, Frost describes the production of tablets by compressing the dosage subunits of Example II and hydroxypropylmethylcellulose in a ratio of 10:1. The rejection asserts this is a formulation having 1% of the hydroxypropylmethylcellulose. Applicants respectfully disagree. Such a formulation constitutes 10% hydroxypropylmethylcellulose. Thus, even if the hydroxypropylmethylcellulose equated with lubricant, which Applicants do not concede, the quantity required by Frost nonetheless exceeds that of the instant claims by a factor of 10. Thus, Frost does not teach or suggest the subject of the instant claims, alone or in combination with Makino.

Makino does not remedy the deficiencies of Frost. The Final Rejection acknowledges that Frost does not teach the compression force of 10-30 kN or the disintegration time of 15 minutes. Without conceding whether Makino provides such a teaching, the point is irrelevant in view of the distinctions of the claimed invention over Frost as discussed above. In order to make a *prima facie* case for obviousness, the rejection must show that Makino provides that which Frost does not. The rejection fails in this respect. Makino does not teach a tablet consisting essentially of neutral microgranules coated only with an active principle mixture and lubricant at less than or equal to 1% (claims 17 & 18); nor does it teach a corresponding active agent premix (claim 11). Further, Makino does not teach or suggest that a tablet can be made as described by Frost but without the "outer pharmaceutically inert component." The absence of any teaching or suggestion that formulations such as those described by Frost can be compounded as tablets without any sustained release matrix material is fatal to a *prima facie* case of obviousness. Applicants respectfully submit that the rejection fails to make a *prima facie* case of obviousness, and that the obviousness rejection must be withdrawn or reversed.

VIII. Claims Appendix

See attached Claims Appendix for a copy of the claims involved in the appeal.

IX. Evidence Appendix

See attached Evidence Appendix for copies of evidence relied upon by Appellant.

X. Related Proceedings Appendix

See attached Related Proceedings Appendix for copies of decisions identified in Section II, supra.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date August 5, 2010

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VIII. CLAIMS APPENDIX

The Appealed Claims

1. (Canceled)

2. (Canceled)

3. (Previously Presented) The tablet of claim 17, wherein the diameter of the neutral microgranules is between 200 and 400 µm.

4. (Previously Presented) The tablet of claim 17, wherein its hardness is between 0 and 20 daN.

5. (Previously Presented) The tablet of claim 17, wherein its friability is between 0 and 1%.

6. (Previously Presented) The tablet of claim 17, wherein its disintegration time is less than 15 minutes.

7. (Cancelled)

8. (Previously Presented) The tablet of claim 17, wherein the compression excipient includes a lubricant.

9. (Previously Presented) The tablet of claim 8, wherein the lubricant is between 0.125 and 0.75% by weight of the tablet.

10. (Previously Presented) The tablet of claim 17, wherein the amount of active principle is less than 10 mg/g of the tablet.

11. (Previously Presented) A tableting premix for the preparation of a tablet, said premix consisting essentially of:

(a) between 99 and 100% by weight of neutral microgranules coated with an active principle mixture,

wherein said active principle mixture consists essentially of an active principle and an optional binder, and said neutral microgranules consist essentially of 62.5% to 91.5% sucrose and the remainder starch, and

(b) between 0 and 1% by weight of a lubricant, and

wherein the premix is directly compressible.

12. (Previously Presented) The premix of claim 11, wherein the active principle coated on the neutral microgranules is less than 4% by weight of the neutral microgranules.

13. (Previously Presented) A process for the preparation of the tablet of claim 17, comprising direct compression of the composition of claim 11 or 12 by employing a compression force of between 5 and 50 kN.

14. (Previously Presented) The tablet of claim 17 wherein the size of the neutral microgranules is between 200 and 600 µm.

15. (Previously Presented) The tablet of claim 8, wherein the lubricant is about 0.25% by weight.

16. (Previously Presented) A process for the preparation of the tablet of claim 17, comprising direct compression of the composition of claim 11 or 12 by employing a compression force of between 10 and 30 kN.

17. (Previously Presented) A tablet consisting essentially of: neutral microgranules coated with an active principle mixture, and an excipient, wherein:

a) the neutral microgranules consist essentially of 62.5% to 91.5% sucrose with the remainder starch, are spherical of uniform diameter between 100 and 2000 µm, and are directly compressible;

b) the coating of active principle mixture consists essentially of an active principle and an optional binder such that the active principle is less than 40 mg/g of the tablet; and

c) the excipient is a compression excipient at less than 1% by weight of the tablet.

18. (Previously Presented) A tablet consisting essentially of: neutral microgranules coated with an active principle mixture, an excipient, and a film coating, wherein:

a) the neutral microgranules consist essentially of 62.5% to 91.5% sucrose with the remainder starch, are spherical of uniform diameter between 100 and 2000 μm, and are directly compressible;

b) the coating of active principle mixture consists essentially of an active principle and an optional binder such that the active principle is less than 40 mg/g of the tablet;

c) the excipient is a compression excipient at less than 1% by weight of the tablet; and

d) the film coating on the tablet restricts exposure of the active principle to light, moisture, or oxygen; or modifies release of the active principle; or modifies the color or appearance of the tablet; or any combination thereof.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.